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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,311	10/31/2003	James McSwiggen	MBHB04-372 (400/137)	9826
20306	7590	06/20/2005	EXAMINER	
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606			WOLLENBERGER, LOUIS V	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/698,311	<b>Applicant(s)</b> MCSWIGGEN ET AL.	
	<b>Examiner</b> Louis V. Wollenberger	<b>Art Unit</b> 1635	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 31 October 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 31 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>325/05, 8/6/04</u> | 6) <input type="checkbox"/> Other: _____  |

*Handwritten signature*

## **DETAILED ACTION**

### ***Priority***

Applicant's claims for continuing application priority under 35 USC §120 and provisional application priority under 35 USC §119(e) are acknowledged. However, International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/393,796, 60/399,348, 60/406,784, 60/408,378, 60/409,293, and 60/440,129 fail to provide adequate support under 35 USC §112 for Claims 1–36 of this application. In the instant case, no support was found in PCT/US03/05028 or the U.S. Provisional Applications listed for claims drawn to double-stranded siNA molecules that down regulate expression of a synuclein-1 (SNCA) gene. If applicant believes that support for claims 1–36, drawn to siNA molecules that down regulate SNCA, is present in the earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

### ***Specification***

Acknowledgment is made of applicants' submission (received on 5/7/2004) of a computer readable form, compact disc copy of the sequence listing in compliance with 37 CFR §1.821–1.825. The Compact Disc, labeled by applicant as "04-732 Sequence Listing", has been entered into the application. Applicants are reminded, however, that pursuant to 37 CFR §1.52(e)(5) and 1.77(b)(4), the specification must be amended to

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add a statement incorporating Compact Disc "04-732 Sequence Listing" by reference. According to 37 CFR §1.52(e)(5) and 1.77(b)(4), the specification must contain, in a separate paragraph, an incorporation-by-reference of the material on the compact disc, identifying the compact disc by the names of the files contained on the compact disc, their date of creation, and their size in bytes. Accordingly, the specification is objected to since it lacks such incorporation-by-reference. Correction is required.

### ***Claims***

Attention is drawn to Claim 31, which appears to contain a typo: "comprisess".

### ***Claim Rejections - 35 USC § 112 and §101***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 provides for the use of a double-stranded short interfering nucleic acid (siNA) molecule to down regulate expression of a SNCA gene, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

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2. Claim 36 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).
3. Claims 13–15 and 18–20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 14, which appear to be missing the indefinite article “the” just after the word “wherein,” recite the limitations “wherein pyrimidine nucleotides” and “ wherein purine nucleotides,” respectively. For purposes of this examination, “the” is presumed to present. Thus, these recitations lack antecedent basis. Claims 15 and 18 recite the limitation “wherein the pyrimidine nucleotides” in relation to the siNA molecule of Claim 6. There is insufficient antecedent basis for this limitation in the claim. Claims 19 and 20 recite the limitation “ wherein the purine nucleotides” in relation to the siNA molecule of Claim 6. There is insufficient antecedent basis for this limitation in the claim.
4. Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “base-paired to” renders the claims indefinite, since it is unclear how double stranded siNAs may remain double

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stranded while at the same time being "base-paired to" an SNCA target RNA.

Replacing the phrase "base-paired" with -- complementary -- would be remedial.

5. Claims 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to compositions; namely, a "medicament" and an "active ingredient" comprising the siNA molecule of claim 1. However, Claims 34 and 35 represent improper composition claims since they recite only one element. Compositions must, by definition, contain two or more elements. See claim 33, for example. Further notice is made of the absence of articles "a" or "an" from each of independent claims 34 and 35. These articles are needed to make grammatical connection to the subject "What we claim is:"

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1–35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.
2. MPEP 2163 states in part that:

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"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)."

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)."

3. For convenience, Claims 1, 31, and 32, the only independent claims, are reproduced below.

1. A double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a synuclein-1 (SNCA) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs.
31. A double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SNCA gene, wherein said siNA molecule comprises no ribonucleotides and wherein each strand of said double-stranded siNA molecule comprises about 21 nucleotides.
32. A double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SNCA gene, wherein said siNA molecule does not require the presence of a ribonucleotide within the siNA molecule for inhibition of SNCA gene.

4. Claim 1 is drawn to short, double-stranded, interfering nucleic acid (siNA) molecules that down regulate "a synuclein-1 (SNCA) gene." Claims 2-30, and 33-35 limit Claim 1 by reciting physical characteristics of the siNA such as the presence or

absence of ribonucleotides, 3' overhangs, 2'-sugar modifications, phosphorothioate internucleotide linkages, and terminal cap structures. The use of the indefinite article in the phrase "a synuclein-1 (SNCA) gene" gives Claim 1 a broad scope that encompasses synuclein-1 (SNCA) from any species as well as any isoform or variant of SNCA from any species.

5. Claims 31 and 32 are interpreted as Claim 1 above, but limited to siNAs having no ribonucleotides.
6. As defined by applicant (page 75, line 13), "PARK1" or "SNCA" is any synuclein or mutant synuclein protein, peptide, or polypeptide having synuclein activity. As defined by applicant (page 76, lines 1–4), "mutant" is any polynucleotide or polypeptide sequence that differs from a wild type polynucleotide or polypeptide sequence. The mutant polynucleotide or polypeptide sequence can be associated with a disease state, such as Parkinson's disease. As defined by applicant (pp. 7–8, and 121) "mutant synucleins" are considered to include any SNCA polymorphic variant or isoform such as the alpha-, beta- and gamma-synucleins, found in humans.
7. In reciting "a synuclein-1 (SNCA) gene", Claim 1 provides no SEQ ID No. to positively identify the sequence(s) being targeted for down regulation. In the absence of that express limitation, the recitation "a synuclein-1 (SNCA) gene" is considered to embrace any wild-type or mutant, human or non-human synuclein gene.



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8. Furthermore, applicants provide no written description of any "SNCA gene." The term "gene" has a broad scope that includes chromosomal DNA. While all genes encompassed by the claims of the instant application share the characteristic of comprising a synuclein-1 (SNCA) coding sequence, there is insufficient written description of specific structures such as promoters, enhancers, introns, exons, and other regulatory elements found in chromosomal DNA and included by the recitation "gene."
9. A review of the disclosure shows that applicant has adequately described over 200 siNAs, corresponding to SEQ ID. Nos. 1–292, listed in Tables II and III. The specification (page 134, lines 8–11) teaches that these siNAs specifically target a human, alpha-synuclein mRNA transcript, corresponding to RefSeq Accession No. NM\_000345, NM\_000345.2.
10. Adequate written description does not exist in the instant application for siNA sequence(s) directed to human synuclein (SNCA) variants or non-human synuclein (SNCA) homologues. Furthermore, there is no disclosure found in the specification or known in the art that relates the structure of an siNA directed to human SNCA mRNA to the function of down regulating SNCA in another species, or down regulating isoforms or variants of SNCA genes from another species.
11. The siNA species specifically disclosed are not representative of the genus because the genus is highly variant. With the exception of the sequences directed to human alpha-synuclein (SNCA), the skilled artisan cannot envision the detailed structure of

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the encompassed siNAs directed to any SNCA, regardless of the complexity or simplicity of the method of isolation.

12. Although some of the siNA sequences, corresponding to SEQ ID Nos. 173–248, in Table II, are preceded with the heading "SNCA 000345.2 Mutants," it is unclear, upon reviewing the specification, what these mutant sequences correspond to. It cannot be determined if these siNAs (SEQ ID Nos. 173–248) are directed to specific, readily identifiable isoforms or mutant variants of human SNCA or if they are simply non-specific variations of the wild-type siNAs, corresponding to SEQ ID Nos. 1–172. If such written description exists in the instant application, applicant is invited to point out with particularity where such written description may be found.
13. Therefore, in the absence of convincing evidence to the contrary, only claims to siNA sequences directed to human SNCA RNA (Isoform NM\_000345.2), but not the full genus of siNAs that down regulate "a synuclein gene," meet the written description requirement of 35 USC 112, first paragraph.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

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only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1, 3–11, 23, 27–30, and 33–35 are rejected under 35 U.S.C. 102(b) as being anticipated by Driscoll and Tavernarakis (2001), WO 01/49844.
2. Claim 1 is drawn to double-stranded, nucleic acid molecules (siNAs) of about 19 to 21 base pairs that down regulate expression of synuclein-1 (SNCA). Claims 3–11, 23, 27–30 limit Claim 1 by reciting siNA molecules comprising 5'-end phosphates, ribonucleotides, and sense and antisense regions, where the antisense region is substantially complementary to the RNA of an SNCA gene. Claims 10–11 limit the invention of Claim 1 to linked molecules—hairpin RNAs, for example, that inhibit synuclein-1 (SNCA) expression. Claims 33–35 recite a pharmaceutical composition, medicament, or active ingredient containing the siNA molecule of Claim 1.
3. Driscoll, WO 01/49844, teaches inverted repeat (IR) gene construct expression vectors encoding short interfering, double-stranded RNAs for down regulating alpha-synuclein gene expression (pp 3–4, Fig. 5) in living cells. The IR expression vectors are assembled from separate sense and antisense fragments, which may each range between 20 and 2500 nucleotides in length (page 11). The cloned fragments are encoded together as a single transcript with a spacer region so that the sense and antisense regions may fold back on one another in the cell to form a double stranded structure. After expression and processing in the cell, the transcript would inherently include 5'-end phosphates. According to WO 01/49844, the IR expression vectors can be generated and then used for the treatment of Parkinson's disease,

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since the dsRNA encoded by such constructs can act to reduce alpha synuclein accumulation (pp. 45–46).

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4. Claims 1 and 33–35 are rejected under 35 U.S.C. 102(e) as being anticipated by Bumcrot et al., International Application Publication WO 2005/004794, effectively filed June 9, 2003
5. WO 2005/004794 teaches RNAi agents that down regulate the expression of alpha-synuclein (SNCA) for the treatment of Parkinson's Disease.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 13–16 and 18–20 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/49844 (2001); WO 03/099298 (2002); and Ueda et al. (1993) *Proc. Natl. Acad. Sci. USA* 90, 11282–11286.
2. WO 01/49844 is relied on for the reasons given above.
3. WO 01/49844 does not teach 2' ribose modifications or terminal cap moieties.
4. WO 03/099298 discloses methods for making and testing short, 19–25 nucleotide, double-stranded RNAs for mediating RNAi in mammalian cells. WO 03/099298 further discloses that dsRNAs may be used to silence alpha-synuclein, and thereby to treat Parkinson's Disease (page 20, lines 21–30; page 69). The dsRNA structures described include those having 3' overhangs or blunt ends (page 55, lines 29–30), terminal 5' phosphates, or hydroxyl groups (page 3, lines 1–11; page 30, lines 25–26), 2' sugar modifications such as 2'-O-methyl, 2'-deoxy, and 2'-fluoro, terminal caps (pp. 31 to 32), and hairpin structures (page 22, lines 18–20; page 31; and pp. 54–61, for example).
5. Ueda et al. (1993) teaches the molecular cloning and nucleotide sequence of the gene coding for human  $\alpha$ (alpha)-synuclein (SNCA), also known as PARK1, a 140-amino acid protein, identified as a precursor protein of the non-A $\beta$ (beta) amyloid component (NAC). NAC is shown to be an intrinsic component of amyloid plaques, proteinaceous inclusions found in patients with Alzheimer's Disease. Ueda et al.

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suggest on page 11286 that, "...NAC might be a factor to promote the process of amyloid formation by serving as a seed or core."

6. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of WO 01/49844, WO 03/099298, and Ueda et al. to make double-stranded nucleic acids capable of down regulating alpha-synuclein. The ordinary artisan would have been both well motivated and would have had a reasonable expectation of success since the techniques for preparing and using short, double stranded interfering nucleic acids were known, the cDNA (i.e., mRNA) sequence of alpha-synuclein (SNCA) was known, and the potential benefit of down regulating SNCA was known.
7. For the above reasons, and in the absence of convincing evidence to the contrary, Claims 13–16 and 18–20 are rejected under 35 USC 103(a) as being unpatentable over International Patent Application Publication WO 01/49844; International Patent Application Publication WO 03/099298; and Ueda et al. (1993) *Proc. Natl. Acad. Sci. USA* 90, 11282–11286.

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8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/49844, WO 03/099298, and Ueda et al. (1993) as applied to Claims 13–16 and 18–20 above, and further in view of U.S. Patent Application Publication 2004/0058886.
9. Claim 12 limits Claim 10, drawn to a short interfering, double-stranded nucleic acid molecules, wherein the sense and antisense regions are connected by a linker

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molecule. Claim 12 adds the limitation wherein the linker molecule, which connects the sense region to the antisense region, is a non-nucleotide linker. For purposes of examination, this limitation is considered to embrace unimolecular hairpin (stem-loop) nucleic acid molecules such as the short hairpin RNAs (shRNAs), described by U.S. Patent Application Publication 2004/0058886, by Scaringe, S.

10. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of WO 01/49844, WO 03/099298, and Ueda et al. (1993) for the reasons described above.

11. WO 01/49844, WO 03/099298, and Ueda et al. (1993) do not teach the use of short hairpin RNAs having non-nucleotide loops, or linkers.

12. U.S. Patent Application Publication 2004/0058886, entitled " Short interfering RNAs having a hairpin structure containing a non-nucleotide loop," teaches short interfering RNA having the structure  $X_1$ -L-  $X_2$ , wherein  $X_1$  and  $X_2$  are nucleotide sequences that form a double-stranded stem and L is a non-nucleotide linker molecule, forming a loop region.

13. In view of such detailed teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce RNAi reagents having the physical and chemical characteristics recited in Claim 12. The ordinary artisan would have been both well motivated and would have had a reasonable expectation of success of producing functional RNAi reagents, since the prior art taught that shRNAs containing such physical and chemical features possess functionality as interfering agents.

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14. For the above reasons, and in the absence of convincing evidence to the contrary,

Claim 12 is rejected under 35 USC 103(a) as being unpatentable over WO 01/49844, WO 03/099298, Ueda et al. (1993), and U.S. Patent Application Publication 2004/0058886.

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15. Claims 17 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over

WO 01/49844, WO 03/099298, and Ueda et al. (1993), as applied to Claims 13–16 and 18–20 above, and further in view of Parrish et al. (2000) *Molecular Cell*, 6, 1077–1087; and U.S. Patent 5,998,203 to Matulic-Adamic (1999).

16. Claims 17 and 21 limit Claims 16 and 18, drawn to capped or 2' modified double-stranded siNA molecules, further defining such molecules that contain phosphorothioate internucleotide linkages and terminal cap moieties.

17. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of WO 01/49844, WO 03/099298, and Ueda et al. (1993) for the reasons described above.

18. WO 01/49844, WO 03/099298, and Ueda et al. (1993) do not teach siNAs with phosphorothioate internucleotide linkages at the 3' end of the antisense region, or siNAs capped with inverted deoxy abasic moieties.

19. Parrish et al. (2000) teaches that some common nucleotide modifications, including phosphorothioate and 2'-sugar modifications are tolerated in interfering RNAs (page 1081).



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20. U.S. Patent 5,998,203 teaches terminal cap modifications, including inverted abasic nucleotides, for incorporation into the 5' and/or 3' ends of ribozymes to improve the efficacy of the ribozyme (Figs. 11A-11B; also, columns 2-4, 8). The modifications are taught as being useful to improve the stability of the ribozyme *in vitro* and *in vivo* by protecting the ribozyme from exonuclease digestion.

21. In view of such detailed teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce RNAi reagents having the physical and chemical characteristics recited in Claims 17 and 21. The ordinary artisan would have been both well motivated and would have had a reasonable expectation of success of producing functional RNAi reagents, since the prior art taught that dsRNAs and ribozymes containing such physical and chemical features have enhanced properties such as increased resistance to nuclease degradation, resulting in enhanced efficacy.

22. For the above reasons, and in the absence of convincing evidence to the contrary, Claims 17 and 21 are rejected under 35 USC 103(a) as being unpatentable over WO 01/49844, WO 03/099298, and Ueda et al. (1993), and further in view of Parrish et al. (2000), and U.S. Patent 5,998,203 to Matulic-Adamic (1999).

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23. Claims 2, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/49844, WO 03/099298, and Ueda et al. (1993), as applied to Claims 13-16 and 18-20 above, and further in view Voinnet et al. (1998) *Cell* 95:177-187.

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24. Claims 2, 31, and 32 are drawn to double-stranded siNA molecules, comprising about 19 to about 21 nucleotides, that down regulate expression of synuclein-1 (SNCA), wherein the siNA molecule contains no ribonucleotides or does not require the presence of ribonucleotides for inhibition of SNCA gene expression.
25. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of WO 01/49844, WO 03/099298, and Ueda et al. (1993) for the reasons described above.
26. WO 01/49844, WO 03/099298, and Ueda et al. (1993) do not teach siNAs having no ribonucleotides.
27. Voinnet et al. (1998) teaches promoterless, double stranded, deoxyribonucleic acid (dsDNA) molecules that induce sequence-specific gene silencing in plants, a eukaryotic organism.
28. In view of such detailed teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce RNAi reagents having the physical and chemical characteristics recited in Claims 2, 31, and 32. The ordinary artisan would have been both well motivated and would have had a reasonable expectation of success of producing functional RNAi reagents, since the prior art taught that dsRNAs, antisense oligos, and ribozymes containing such physical and chemical features have enhanced properties such as increased resistance to nuclease degradation, resulting in enhanced efficacy.
29. For the above reasons, and in the absence of convincing evidence to the contrary, Claims 2, 31, and 32 are rejected under 35 USC 103(a) as being unpatentable over

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WO 01/49844, WO 03/099298, Ueda et al. (1993), and further in view of Voinnet et al. (1998).

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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